REMARKS

Claims 1-19 are pending in this application. Claims 7, 8, and 11-14 have been withdrawn. Claims 1-4, 6, 9-10, and 15 have been amended, and claims 16-19 are new. Support for the amendments to claim 1 can be found in the specification, for example, on page 5, lines 26-27; on page 6, lines 14-17; on page 8, lines 6-9; and on page 23, lines 18-22. Support for these amendments is also present in the PCT priority document (WO 01/14551), e.g., on page 6, lines 2-4; on page 6, lines 26-30; on page 8, lines 21-26; and on page 23, lines 18-23. Support for the amendments to claims 6 and 15 can be found in the specification, for example, on page 16, lines 28-29, and in the PCT priority document, e.g., on page 16, lines 1-2. Support for the amendment to claim 9 can be found, for example, on page 24, lines 5-6, and in the PCT priority document, e.g., on page 24, lines 3-5. New claims 16-18 are derived from claim 1. Support for new claim 19 can be found in the specification, for example, on page 34, lines 15-17, and in the PCT priority document, e.g., on page 35, lines 10-13. No new matter has been added.

Restriction Requirement

Applicants note that the restriction requirement has been modified to include SEQ ID NO:11 (encoding SEQ ID NO:12) in the present restriction group. The claims have been amended to eliminate non-elected SEQ ID NOs: 13 and 14. Applicants respectfully request rejoinder of withdrawn claim 8 upon allowance of the claims under examination.

35 U.S.C. § 101 Utility

The Office Action alleges that claims 1-6, 9-10, and 15 lack a well-established or specific and substantial utility. Applicants respectfully request that this rejection be withdrawn, because according to the standards set forth in the U.S. Patent and Trademark Office's Revised Interim Utility Guidelines Training Materials of 1999 ("Utility Guidelines"), a utility exists.

The nucleic acid sequences recited in claim 1 have specific and substantial utility. Following the flowchart set forth on page 9 of the Utility Guidelines, the first inquiry is whether or not the applicant has made any assertion of utility. Indeed, Applicants have made an assertion of utility for the invention. Multiple utilities are described on page 3, lines 25-30 of the specification:

> The novel bHLH type transcription factors "DEC2" isolated by the present inventors are thought to be members of the DEC1 subfamily. Consequently, they are expected to be useful as novel factors that control development and tissue differentiation. It is also expected that they may be used as markers to determine developmental stages and cell differentiation. Additionally, they are expected to be useful as targets in developing pharmaceutical agents for various diseases associated with the proteins of the present invention. (emphasis added)

As further stated on page 5, lines 7-22 of the specification:

> The present invention provides novel bHLH type transcription factors and DNA encoding the proteins. The nucleotide sequences of the cDNA of bHLH type transcription factors, human DEC2a, human DEC2b, and mouse DEC2a (collectively called "DEC2") isolated by the present inventors, and the amino acid sequences of the proteins encoded by the cDNA are shown in SEQ ID NO:1, 11, 13, 2, 12, and 14, respectively. The "DEC2" genes isolated by the present inventors are suggested to be related not only to differentiation and proliferation of tissues including cartilages, but also to functions of various adult tissues since they were highly homologous to bHLH type transcription factor SHARP in the bHLH region, which is suggested to be involved in the plasticity of cells of the central nervous system in rats. Thus, "DEC2" proteins of the present invention and DNA encoding these proteins are not only useful as factors that control tissue differentiation and cell function, or as differentiation markers, but they may also be applied to the diagnosis, prophylaxis, and treatment of diseases related to the proteins of the present invention.
>
> For example, "DEC2" is important in elucidating the differentiation and deformation mechanisms of cartilages, and it is also expected to be useful in developing gene therapy methods against osteoarthritis, rheumatoid arthritis, etc. (emphasis added)

Claim 1, which recites nucleic acid sequences, is similar to Example 10 of the Utility Guidelines. Example 10 of the Utility Guidelines presents a claim to "An isolated

and purified nucleic acid comprising SEQ ID NO:2." The Example states that SEQ ID NO:2 has a high level of homology to a DNA ligase, and also states:

> The specification teaches that SEQ ID NO:2 encodes SEQ ID NO:3. An alignment of SEQ ID NO:3 with known amino acid sequences of DNA ligases indicates that there is a high level of sequence conservation between the various known ligases. The overall level of sequence similarity between SEQ ID NO:3 and the consensus sequence of the known DNA ligases that are presented in the specification reveals a similarity score of 95% ... Based on the sequence homologies, the specification asserts that SEQ ID NO:2 encodes a DNA ligase.

The nucleic acid sequences of claim 1 also encode proteins. The proteins encoded by the nucleic acid sequences of claim 1 have a high level of sequence identity to bHLH transcription factors in the N-terminal half of the sequence, which contains the region that identifies the protein as a bHLH transcription factor. As stated on page 3, lines 13-18, of the specification:

> The amino acid sequence of human DEC2a showed the highest similarity to that of rat SHARP-1. Particularly, the N-terminus half was 90% or more identical ... This protein was supposed to be a new member of the DEC1 subfamily, because the bHLH region showed a high similarity. (emphasis added)

The bHLH domains of proteins encoded by the nucleic acid sequences of claim 1 have greater than 90% identity to a known bHLH domain; Example 10 of the Utility Guidelines makes it clear that 95% similarity is sufficient. Thus, the sequence similarity of the proteins encoded by the nucleic acid sequences recited in claim 1 to known bHLH domains is similar to the levels set forth in Example 10.

According to Example 10:

> Based upon applicant's disclosure and the results of the PTO search, there is no reason to doubt the assertion that SEQ ID NO:2 encodes a DNA ligase. Further, DNA ligases have a well-established use in the molecular biology art based on this class of protein's ability to ligate DNA. Consequently, the answer to the question is yes.

Following the rationale set forth in Example 10, there is no reason to doubt the assertion that the nucleic acid sequences of claim 1 encode a bHLH transcription factor, because there is greater than 90% identity between the bHLH domains of the proteins they encode and known bHLH domains. Further, bHLH transcription factors are known to function to regulate transcription. As stated on page 1, lines 14-19, of the specification:

> bHLH (basic domain-Helix-Loop-Helix structure) type transcription factors are reported to control cell proliferation and differentiation in myogenesis (Weintraub et al., Science 251:761-6, 1991), neurogenesis (Jan et al., Cell 75:827-830, 1993), hematopoiesis (Zhuang et al., Cell 79:875-884, 1994), and such. bHLH type transcription factors are characterized by a conserved region (bHLH structure) of 60 to 70 amino acids, which mediates dimer formation of proteins.

This utility is further substantiated by Azmi et al., J. Biol. Chem. 279:52643-52652, 2004 (a copy of which is provided herewith), which demonstrates that murine Sharp-1 [DEC2] inhibits skeletal muscle differentiation by interacting with and inhibiting the function of MyoD and E-protein transcription factors. Therefore, the claimed nucleic acid sequences have an asserted utility based on the high level of sequence similarity among the bHLH domains of the proteins they encode and other known bHLH domains.

The next inquiry is whether the assertion identifies a specific utility. Applicants' asserted utility is specific. According to the Utility Guidelines, a utility is specific in the sense that it "contrasts with a *general* utility that would be applicable to the broad class of the invention" (page 5). The "broad class" of the invention here is nucleic acids. As stated above, the nucleic acids encompassed by claim 1 encode transcription factors that "are expected to be useful as novel factors that control development and tissue differentiation" (specification, page 3, lines 26-27). This utility is specific to the nucleic acid sequences recited in the claims, because not all nucleic acids encode transcription factors, and because not all transcription factors are expected to control development and tissue differentiation. It is not a utility applicable to the broad class of the invention (i.e.,

all nucleic acids in general). Thus, it meets the "specific" criterion of the Utility Guidelines.

The next inquiry is whether the assertion identifies a substantial utility. According to the Utility Guidelines, a utility is substantial if it defines a "real world" use (page 6). The specific utility asserted by Applicants is substantial because it does define a real world use: The proteins encoded by the sequences recited in the claims are transcription factors and are expected to control development and tissue differentiation. Given their role in differentiation of cartilaginous tissues, they can be used for screening for substances useful in treating conditions such as osteoarthritis and rheumatoid arthritis.

The final inquiry is whether this asserted, specific, and substantial utility is credible. The Utility Guidelines state on page 5 that "[a]n assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion." The Examiner has not provided any evidence that the logic of Applicants' assertion of utility is flawed and thus has not met the *prima facie* burden of showing a lack of utility:

> Where the asserted specific and substantial utility is not credible, a *prima facie* showing of no specific and substantial credible utility must establish that it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted by the applicant for the claimed invention. (MPEP § 2107.02 (IV)).

Applicants respectfully request that this rejection, and the related lack of utility rejection under 35 U.S.C. § 112, 1st paragraph, of claims 1-6 and 15 be withdrawn.

Claim 10, as amended, recites an isolated nucleic acid that has a homology of at least 70% to the sequence of SEQ ID NO:1 or 11 and encodes a polypeptide that comprises a bHLH domain and functions as a bHLH type transcription factor. Applicants have demonstrated the utility of the nucleic acids of SEQ ID NOs:1 and 11. Because claim 10 recites a nucleic acid that has at least 70% identity with SEQ ID NO:1 or 11, this claim derives its utility from the utility of SEQ ID NOs:1 and 11. Because the nucleic acid of claim 10 has at least 70% identity with SEQ ID NO:1 or 11, possesses a

bHLH domain, and functions as a bHLH type transcription factor, the nucleic acid has utility for the same uses as SEQ ID NOs:1 and 11, e.g., for screening for substances useful in treating conditions such as osteoarthritis and rheumatoid arthritis. Thus, Applicants respectfully request that this rejection, and the related lack of utility rejection under 35 U.S.C. § 112, 1st paragraph, of claim 10 be withdrawn.

The Office Action also alleges that claim 9 lacks utility. Claim 9, as amended, recites an isolated nucleic acid comprising at least 15 nucleotides, wherein the nucleic acid is completely complementary to (a) at least a portion of a nucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NOs:1 and 11 that includes the translation initiation codon of SEQ ID NO:1 or 11, respectively, or (b) to the complementary strand of (a). As discussed above, Applicants have demonstrated the utility of the nucleic acids of SEQ ID NOs:1 and 11. Because claim 9 recites a nucleic acid that includes at least 15 nucleotides of SEQ ID NO:1 or 11, this claim derives its utility from the utility of SEQ ID NOs:1 and 11. The nucleic acid has utility, for example, as a probe or PCR primer to identify SEQ ID NO:1 or 11 (or its complement) in a cDNA library. Thus, Applicants respectfully request that this rejection, and the related lack of utility rejection under 35 U.S.C. § 112, 1st paragraph, of claim 9 be withdrawn.

35 U.S.C. § 101 Statutory Subject Matter

The Office Action alleges that claims 6 and 15 are drawn to non-statutory subject matter due to the use of the term "transformant." Applicants have amended claims 6 and 15 to recite "transformant cell," as suggested by the Examiner, and respectfully request that this rejection be withdrawn.

35 U.S.C. § 112, 1st Paragraph

The Office Action alleges that claims 1-6 and 15 fail to satisfy the written description requirement because possession of the claimed invention was not shown. Specifically, the Office Action alleges that "because the specification fails to describe the

specific biological function of the wild type proteins (which are presumably present in the proteins), the specification does not describe the structure of even one variant sequence which retains the biological activity" (page 11). Applicants respectfully disagree, because biological functions of the claimed proteins and variants of SEQ ID NOs:2 and 12 are described in the specification, e.g, on page 5, line 26 through page 6, line 2:

> Herein, "functionally equivalent" means that the target protein has a function of a bHLH type transcription factor. The function of a bHLH type transcription factor is to form a homodimer (or a heterodimer with other bHLH type transcription factors) and have an activity to negatively or positively regulate transcriptional activity. Further, a bHLH type transcription factor may have a binding activity towards CANNTG and/or CACNAG. Methods for measuring the binding activity towards CANNTG and/or CACNAG are well known (for example, Ohsako et al., Genes & Dev. 8:2743-2755, 1994).

However, to facilitate prosecution, Applicants have amended claims 1(c) and 1(d) to require that any variant nucleic acid encode a polypeptide that both (A) includes a bHLH domain and (B) functions as a bHLH transcription factor. This combination of elements adds both structural and functional limitations to the relevant parts of the claims, in line with the written description in the specification.

The Office Action alleges that "there is no guidance as to the parts of the sequences that need to be unaffected in order to retain the biological activity of the proteins" (pages 11-12). Applicants respectfully disagree. The specification provides considerable guidance as to which amino acid residues of the proteins can and cannot be varied, as discussed below.

Figure 4 of the specification provides an alignment of human DEC2a (hDEC2a; SEQ ID NO:2), murine DEC2a (mDEC2a; SEQ ID NO:14), and the rat SHARP-1 protein. This alignment shows which amino acid positions among these three related proteins do not vary and which positions do vary. The alignment also shows which positions tolerate only conservative variations and which positions can tolerate non-

conservative variations. For example, position 124 of hDEC2a is occupied by a isoleucine (I) residue; the same position in mDEC2a and SHARP-1 is occupied by a valine (V) residue. As described on page 6, lines 18-26, both isoleucine and valine possess aliphatic side chains, indicating that this is a conservative variation. In contrast, position 126 in hDEC2a is occupied by a serine (S) residue; the same position in mDEC2a and SHARP-1 is occupied by an alanine (A) residue. Serine possesses a hydroxyl group on its side chain; alanine possesses an aliphatic side chain. This represents a non-conservative variation and indicates that position 126 can be varied with non-conservative amino acid changes (and presumably conservative ones as well). Position 125 in all three proteins is occupied by a glutamine (Q) residue, indicating that this position is likely to be one that should not be varied. Thus, by providing sequence alignments, the specification does teach which positions of the sequence can and cannot be varied.

The Examiner acknowledges at page 13 of the Office Action that nucleic acids encoding SEQ ID NO:2 or 12 or fragments thereof "meet the written description provision of 35 U.S.C. 112, first paragraph." This acknowledgement applies to parts (a), (b), and (e) of claim 1, as well as claim 9 and new claims 16-19. In view of the above arguments, Applicants submit that all parts of all of the pending claims are fully supported by adequate written description. Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. § 112, 2nd Paragraph

The Office Action alleges that claims 1-6 and 15 are indefinite because of the use of the term "stringent conditions" in claim 1. Applicants have amended part (d) of claim 1 to recite the specific hybridization conditions under which the recited nucleic acid sequence must hybridize to the disclosed sequences. Applicants submit that the amendment renders the claim definite and respectfully request that this rejection be withdrawn.

35 U.S.C. § 102(b)

The Office Action alleges that claims 1-6, 9-10, and 15 are anticipated by NCI-CGAP (Accession No. AA996006/c). Applicants respectfully disagree because this cited nucleic acid sequence does not teach the full length nucleic acid sequences or the function of the proteins encoded by the nucleic acids recited in the claims.

The Office Action states that "NCI-CGAP teaches an isolated nucleic acid (a cDNA clone and corresponding mRNA) which comprises 100% sequence similarity to 322 contiguous nucleotides of SEQ ID NO:1 and SEQ ID NO:11" (page 15). Applicants will discuss each part of claim 1 separately.

Claim 1(a), as amended, recites "a nucleic acid comprising the coding region of a nucleotide sequence selected from the group consisting of SEQ ID NO:1 and 11." NCI-CGAP is 432 nucleotides in length and contains a 322-nucleotide portion that is identical to 322 nucleotides of each of SEQ ID NOs:1 and 11. The entire coding regions of SEQ ID NOs:1 and 11 are 1446 and 1452 nucleotides in length, respectively. Because much of SEQ ID NOs:1 and 11 was not present in the NCI-CGAP sequence, a claim specifying SEQ ID NO:1 or 11 cannot be anticipated by NCI-CGAP. Thus, part (a) is free of the art (as is new claim 16).

Claim 1(b), as amended, recites "a nucleic acid encoding a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO:2 and 12." SEQ ID NOs:2 and 12 are 482 and 484 amino acids long, respectively; they are encoded by coding regions that are 1446 and 1452 nucleotides in length, respectively. Thus, the 432 nucleotide-long NCI-CGAP cannot anticipate a nucleic acid that encodes a protein that comprises SEQ ID NO: 2 or 12. Part (b) of claim 1 is therefore free of the art (as are new claims 17 and 18).

Claim 1(c), as amended, recites "a nucleic acid encoding a protein comprising a modified sequence of an amino acid sequence selected from the group consisting of SEQ ID NOs:2 and 12, wherein the protein encoded by said nucleic acid comprises a bHLH

domain, functions as a bHLH type transcription factor, and differs from SEQ ID NO:2 or 12, respectively, by mutation at no more than 100 positions." SEQ ID NOs: 2 and 12 are 482 and 484 amino acids long, respectively. Even if 100 positions of either of these sequences were altered or deleted, the proteins would still have 382 and 384 amino acids of SEQ ID NO:2 or 12, respectively, that were not altered or deleted. The 322-nucleotide region of NCI-CGAP that is identical to 322 nucleotides of SEQ ID NOs:1 and 11 can encode only 107 amino acids of SEQ ID NO:2 or 12. Thus, NCI-CGAP does not anticipate the nucleic acid recited in claim 1(c).

Claim 1(d), as amended, recites "a nucleic acid that (i) hybridizes in 6x SSC (0.9 M sodium chloride, 0.09 M sodium citrate), 0.5% SDS, 10 mM EDTA, 5x Denhardt's solution (0.1% (w/v) Ficoll, 0.1% (w/v) polyvinylpyrrolidone, 0.1% (w/v) BSA), 10 mg/ml denatured salmon sperm DNA at 60° to a probe consisting of the complement of a nucleotide sequence selected from the group consisting of SEQ ID NOs:1 and 11, (ii) is at least 90% identical to SEQ ID NO:1 or 11, and (iii) encodes a protein that comprises a bHLH domain and functions as a bHLH type transcription factor." The entire coding regions of SEQ ID NOs:1 and 11 are 1446 and 1452 nucleotides in length, respectively. A nucleic acid sequence that is at least 90% identical to SEQ ID NOs:1 and 11 would be identical to at least 1301 and 1306 nucleotides, respectively, over the length of SEQ ID NOs:1 and 11. It is not possible for the 322 nucleotides of NCI-CGAP to have this degree of sequence identity to SEQ ID NOs:1 and 11. Thus, NCI-CGAP does not anticipate the nucleic acid of claim 1(d).

Claim 1(e), as amended, recites "a nucleic acid encoding a partial peptide of a protein selected from the group consisting of SEQ ID NOs:2 and 12 that differs from the sequence of one of SEQ ID NO:2 or 12 at no more than 100 positions." SEQ ID NOs: 2 and 12 are 482 and 484 amino acids long, respectively. The claimed polypeptide would have to be at least 382 or 384 residues in length, respectively. At most, NCI-CGAP can encode a total of 107 amino acids identical to part of SEQ ID NO:2 or 12. Thus, NCI-CGAP does not anticipate the nucleic acid of claim 1(e).

Claim 9, as amended, recites "An isolated nucleic acid comprising at least 15 nucleotides, wherein the nucleic acid is completely complementary (a) to at least a portion of a nucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NOs:1 and 11 that includes the translation initiation codon of SEQ ID NO:1 or 11, respectively, or (b) to the complementary strand of (a)." The nucleotide sequence of NCI-CGAP that is identical to part of SEQ ID NOs: 1 and 11 begins at nucleotide 370 of SEQ ID NO:1 (i.e., 235 nucleotides downstream of the translation initiation codon of SEQ ID NO:1) and nucleotide 243 of SEQ ID NO:11 (i.e., 241 nucleotides downstream of the translation initiation codon of SEQ ID NO:11). Therefore, NCI-CGAP does not contain a sequence identical to a portion of SEQ ID NO:1 or 11 containing the translation initiation codon of SEQ ID NO:1 or 11 and does not anticipate claim 9.

Claim 10, as amended, recites "An isolated nucleic acid that has a homology of at least 70% to the sequence of SEQ ID NO:1 or 11 and encodes a polypeptide that comprises a bHLH domain and functions as a bHLH type transcription factor." The entire coding regions of SEQ ID NOs:1 and 11 are 1446 and 1452 nucleotides in length, respectively. A nucleic acid sequence that has a homology of at least 70% to the sequence of SEQ ID NO:1 or 11 would be identical to at least 1012 and 1016 nucleotides, respectively, over the length of SEQ ID NOs:1 and 11. It is not possible for the 322 nucleotides of NCI-CGAP to have this degree of homology to SEQ ID NOs:1 and 11. Thus, NCI-CGAP does not anticipate the nucleic acid of claim 10.

Because NCI-CGAP does not fall within any of claims 1, 9, and 10, it does not anticipate any of claims 1-6, 9-10, and 15-19. Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants respectfully submit that the rejections to claims 1-6, 9-10, and 15 have been overcome by the amendments and arguments presented herein, and request that the rejections be withdrawed.

Enclosed is a $200 check for excess claim fees and a $1,020 check for the Petition for Extension of Time fee. Apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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